Docket No.: 134391.00115
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Per Holm *et al.*

Application No.: 10/569,863 Confirmation No.: 9762

Filed: June 13, 2006 Art Unit: 1614

For: SOLID DISPERSIONS COMPRISING TACROLIMUS Examiner: G. Polansky

DECLARATION OF PER HOLM UNDER 37 C.F.R. §1.132

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Per Holm, do hereby declare and state as follows:

1. I have read and am familiar with the present application as it was filed in the U.S. Patent and Trademark Office ("USPTO") on June 13, 2006, and the claims as amended by an accompanying Amendment. A listing of the amended claims is attached as Exhibit A.

2. The claims of the present application are directed to solid pharmaceutical compositions containing a combination of polyethylene glycol and a poloxamer. Claim 1 of the present application, as amended by the accompanying Amendment, reads as follows:

> 1. A solid pharmaceutical composition comprising tacrolimus in polyethylene glycol having an average molecular weight of at least 1500 and a poloxamer, wherein the tacrolimus, polyethylene glycol and poloxamer are on a solid carrier, wherein the tacrolimus is present therein

in a concentration of between 0.01 w/w% and 15 w/w%, wherein the solid pharmaceutical is in particulate form.

3. I am the sole inventor of the subject matter claimed in the present application.

4. I further understand that the present application stands rejected as obvious over International Publication No. WO 03/04001 ("WO '001"), which was published on January 16, 2003.

5. The face of WO '001 lists Anders Buur, Michiel Onne Elema, Birgitte Møllegaard, Jannie Egeskov Holm, Kirsten Schultz, and me as inventors.

6. WO '001 discloses and claims, among other things, a method for the preparation of a particulate material by controlled agglomeration.

7. I am the sole inventor of the disclosure in WO '001 of compositions containing a combination of polyethylene glycol and a poloxamer.

8. Anders Buur, Michiel Onne Elema, Birgitte Møllegaard, Jannie Egeskov Holm and Kirsten Schultz are not co-inventors of the compositions containing a combination of polyethylene glycol and a poloxamer.

9. I further declare that all statements made herein are based on information and belief and are believed to be true and that these statements were made with the knowledge that willful false statements made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

12-Aug-2010
Date

Per Holm
Per Holm

EXHIBIT A

1. A solid pharmaceutical composition comprising tacrolimus in polyethylene glycol having an average molecular weight of at least 1500 and a poloxamer, wherein the tacrolimus, polyethylene glycol and poloxamer are on a solid carrier, wherein the tacrolimus is present therein in a concentration of between 0.01 w/w% and 15 w/w%, wherein the solid pharmaceutical is in particulate form.

2. (Canceled)

3. The solid pharmaceutical composition according to claim 1, wherein the tacrolimus is partly dissolved in the polyethylene glycol and the poloxamer to form a mixture of solid dispersion and solid solution at ambient temperature.

4. The solid pharmaceutical composition according to claim 1, wherein the tacrolimus is fully dissolved in the polyethylene glycol and the poloxamer to form a solid solution at ambient temperature.

5. The solid pharmaceutical composition according to claim 1, wherein the polyethylene glycol and the poloxamer has a melting point of at least 30 °C.

6. The solid pharmaceutical composition according to claim 1, wherein the concentration of tacrolimus in the vehicle is at the most 10w/w%.

7. The solid pharmaceutical composition according to claim 1, wherein the concentration of tacrolimus in the vehicle is at least 0.05w/w%.

8. The solid pharmaceutical composition according to claim 1, wherein at least 50 w/w% of the tacrolimus is released within 30 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.

9. The solid pharmaceutical composition according to claim 1, wherein at least 75 w/w% of the tacrolimus is released within 40 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.

10. The solid pharmaceutical composition according to claim 1, wherein at least 90 w/w% of the tacrolimus is released within 60 minutes, when tested in any dissolution test according to USP using an aqueous dissolution medium.

11-15. (Canceled)

16. The solid pharmaceutical composition according to claim 1, wherein the mixture comprises a polyethylene glycol and a poloxamer in a proportion of between 1:3 and 10:1.

17. The solid pharmaceutical composition according to claim 16, wherein the poloxamer is poloxamer 188.

18. The solid pharmaceutical composition according to claim 16, wherein the polyethylene glycol has an average molecular weight of about 6000 (PEG6000).

19. The solid pharmaceutical composition according to claim 1, comprising one or more pharmaceutically acceptable excipients.

20. The solid pharmaceutical composition according to claim 19, wherein the pharmaceutically acceptable excipients are selected from the group consisting of fillers, disintegrants, binders and lubricants.

21. (Canceled)

22. The solid pharmaceutical composition according to claim 1, wherein the particles have a geometric weight mean diameter d_{gw} from 10 μm to 2000 μm.

23. The solid pharmaceutical composition according to claim 1, wherein the particles have a geometric weight mean diameter d_{gw} from 50 μm to 300 μm.

24. A solid dosage form comprising the solid pharmaceutical composition according to claim 19, which is a solid oral dosage form.

25. The solid dosage form according to claim 24, which is a unit dosage form.

26. The solid dosage form according to claim 24, which further comprises a pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents and release modifying agents.

27. The solid dosage form according to claim 24, wherein at least one pharmaceutical acceptable excipient is selected from the group consisting of silica acid or salt thereof.

28. The solid dosage form according to claim 24, wherein at least one pharmaceutically acceptable excipient is a silica acid or salt thereof.

29. The solid dosage form according to claim 24, wherein at least one pharmaceutical acceptable excipient is silicon dioxide or a polymer thereof.

30. (Canceled)

31. The solid dosage form according to claim 26 comprising one or more release modifying agents selected from the group consisting of water-miscible polymers, water-insoluble polymers, oils and oily materials.

32. The solid dosage form according to claim 31, wherein the water-insoluble polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof.

33. The solid dosage form according to claim 31, wherein the oil or oily material is selected from the group consisting of hydrophilic and hydrophobic oils or oily materials.

34. The solid dosage form according to claim 31, wherein the oil or oily material is hydrophilic and selected from the group consisting of polyether glycols and mixtures thereof.

35. (Canceled)

36. The solid dosage form according to claim 31, wherein the oil or oily material is hydrophobic and selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils; higher fatty acid, stearic acid, myristic acid, palmitic acid, higher alcohols, low melting point waxes, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

37. The solid dosage form according to claim 36, wherein the oil or oily hydrophobic material has a melting point of at least 20 °C.

38. The solid dosage form according to claim 31, wherein the water-miscible polymer is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly-s-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA, polymethacrylic polymers and polyvinyl alcohol (PVA), poly (ethylene oxide) (PEO) and mixtures thereof.

39. The solid dosage form according to claim 38, wherein the polymethacrylic polymers are selected among Eudragit® RS, Eudragit® RL, Eudragit® NE and Eudragit® E.

40. The solid dosage form according to claim 31, which is entero-coated using a water-miscible polymer having a pH-dependant solubility in water.

41. The solid dosage form according to claim 40, wherein the water-miscible polymer is selected from the group consisting of polyacrylamides; cellulose acetate phthalate, cellulose

acetate terephtahalate, cellulose acetate isophthalate, cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; polyvinyl acetate phthalate (PVAP); hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers; polyacrylic acid derivatives, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymers, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolat; polacrylin; vinyl acetate and crotonic acid copolymers and mixtures thereof.

42. The solid dosage form according to claim 40, which upon oral administration to a mammal in need thereof releases at the most about 10% w/w of the tacrolimus within the first 3 hours following administration.

43. The solid dosage form according to claim 24, wherein the solid dosage form upon oral administration to a mammal in need thereof provides an AUC or C_{max} of tacrolimus that is 80%-125% of that provided by a capsule dosage form approved under U.S. Food and Drug Administration NDA No. 050708, wherein the dose of tacrolimus administered with the solid dosage form is at the most about 85% w/w of the dose of tacrolimus administered in the form of the capsule dosage form approved under NDA No. 050708.

44. The solid dosage form according to claim 24, wherein the solid dosage form upon oral administration to a mammal in need thereof releases at least 50% w/w of the active ingredient within 24 hours.

45-50. (Canceled)

51. A method for the preparation of the solid pharmaceutical composition according to claim 1, the method comprising the steps of (a) dispersing and/or dissolving tacrolimus in a

polyethylene glycol having an average molecular weight of at least 1500 and a poloxamer to form a mixture, and (b) spraying the mixture onto a solid carrier to obtain the solid pharmaceutical composition.

52. The method according to claim 51, wherein step (a) is performed in the absence of an organic solvent.

53. A solid pharmaceutical composition prepared according to the method of claim 51.

54. A solid pharmaceutical composition prepared according to the method of claim 52.

55. The solid pharmaceutical composition according to claim 1, wherein the solid pharmaceutical composition is a tablet.

56. A solid pharmaceutical composition comprising tacrolimus dispersed or dissolved, in the absence of an organic solvent, in polyethylene glycol having an average molecular weight of at least 1500 and a poloxamer, wherein the tacrolimus is present therein in a concentration of between about 0.01 w/w% and about 15 w/w%, wherein the solid pharmaceutical is in particulate form.

57. The solid dosage form according to claim 31, wherein the release modifying agent is hydroxypropyl methylcellulose (HPMC).